Comparison of hypoxanthine and lactate as indicators of hypoxia in man

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Three general concepts may serve to detect hypoxia in a patient:

1. The oxygen-supply to the tissue can be monitored by parameters of the oxygen-concentration in the blood (e.g. arterial and transcutaneous pO_2 or oxygen-saturation). These parameters are easy to follow but do not detect hypoxia in all conditions (e.g. decreased perfusion).
2. Cellular activity: ECG and CTG are routinely used to detect hypoxia and data linking EEG with cerebral hypoxia are beginning to accumulate (1).
3. Metabolic Products: Lactate, a product of anaerobic glycolysis, is a well accepted parameter of hypoxia (2). Hypoxanthine, a product of anaerobic ATP-catabolism is thought to be accumulated in hypoxia because of its increased production and because its breakdown is also oxygen dependent.

In severe hypoxia in newborn (4) and in animal experiments plasma hypoxanthine was elevated. We confirmed these data but failed to show a relationsship between the severity of the hypoxia in newborn and their plasma hypoxanthine-concentration (3). As other mechanisms might be involved in the hypoxanthine-production of the newborn we turned to the less complex situation of trying to induce pure hypoxia in healthy adults by exposing them to a simulated altitude of 6000 m in a low pressure chamber. Respiration- and ECG- data were collected and venous blood was obtained. Standard methods were used for all determinations except for hypoxanthine which was measured by a method combining xanthine-oxidase with an NADH-producing system (6). In 14 experiments we have found that exposureto an alveolar pO_2 (P_AO_2) of 26 to 33 mmHg during 12 to 56 min. produced a significant increase in lactate but none in hypoxanthine (5). Hypoxia was increased in further 4 volounteers by asking muscle-exercise of 20 Watts during 4 minutes at ground level and at 6000 m. Exposition to minimal pO_2 lasted from 20 to 30 min. and the P_AO_2 reached 31 to 37 mmHg and was lowered to 29 to 33 mmHg by exercise. Table 1 shows that hypoxanthine is not altered by exercise at neither altitude. A significant rise in the lactate concentration is produced by work at 6000 m. Absence of a lactate elevation at 400 m indicates that exercise is below the level inducing hypoxia per se.

Table 1: Changes of lactate, hypoxanthine and blood gases due to exercise at different P_AO_2

Altitude	m	400	6000
P_AO_2	mm Hg	96.4 ± 7.0	34.5 ± 2.5
N		4	4
Changes due to exercise			
Δ Lactate	mg/cl	-0.9 ± 1.4	3.0 ± 1.6 *
Δ Hypoxanthine	µM	1.4 ± 1.9	-0.3 ± 0.6
Δ venous pH		-.007 ± .004	-.003 ± .017
Δ P_ACO_2	mm Hg	0.3 ± 1.6	0.6 ± 0.7

* significant $p < 0.05$

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Unchanged P_ACO_2 excludes hyperventilation as explanation for hyperlactatemia. One might suppose that conversion of hypoxanthine to urate is rapid enough to prevent its accumulation. To investigate this, allopurinole, a xanthine-oxidase inhibitor was used. Increasing purine turnover would then lead to a increased hypoxanthine-level as its degradation is blocked. A further group of 4 volounteers was exposed to hypoxia as outlined above but after three days treatment with allopurinole (3 x 100 mg Zyloric^R daily). The initial hypoxanthine level was elevated to 11.0 ± 5.6 µM (normal 0 to 5 µM). Table 2 shows a significant elevation of lactate upon work at 6000 m but none for hypoxanthine at both levels. Hyperventilation can again be excluded by the P_ACO_2. It is concluded that not only hypoxanthine concentration in the blood but also its production and release into the circulation is unchanged.

Table 2: Changes of lactate, hypoxanthine and blood gases due to exercise at different P_AO_2 after inhibition of the xanthine-oxidase.

Altitude	m	400	6000
P_AO_2	mm Hg	93.5 ± 5.0	32.2 ± 6.3
N		4	4
Changes due to exercise			
Δ Lactate	mg/cl	-0.3 ± 0.5	3.2 ± 1.6*
Δ Hypoxanthine	µM	-2.5 ± 2.7	0 ± 3.5
Δ venous pH		-.006 ± .007	.026 ± .004*
Δ P_ACO_2	mm Hg	0.6 ± 0.8	-0.7 ± 3.1

* significant ($p<0.05$)

The critical pO_2 where hypoxia begins to be detectable on the basis of cellular metabolism can be analyzed by comparing P_AO_2 and lactate. A significant correlation of minimal P_AO_2 and lactate was found in the experiments reported ($p<0.05$). Lowering of the P_AO_2 below 30 to 35 mmHg causes the lactate to increase above its nomal range.

From these experiments with healthy adults we conlude:

1. Neither hypoxanthine-concentration in the blood nor its production rate is increased under mild hypoxic conditions where lactate already indicates hypoxia.
2. Altitude and exercise induced hypoxemia reaches a critical level of oxygen supply as monitored by the lactate production at a P_AO_2 of about 30 to 35 mm Hg.

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